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| EXAMINER | |
|---|---|
| LEITH, PATRICIA A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1655 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/743,170 | ESPERESTER ET AL. | |
| | Examiner | Art Unit | |
| | Patricia Leith | 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *1/26/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,5-16,29,30,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-16,29,30 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/26/2010 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office Action.

### *Request to Remove Finality of Previous Office action*

Applicants request the removal of finality of the previous final Office action mailed 10/01/2009 due to the inadvertent omission from examination of claims 34-35 newly added in the amendment filed June 10, 2009 (Remarks, p. 7). However, Applicants' request is not timely (37 CFR 1.181(f)). A request for withdrawal of finality must be either agreed to by the Examiner (whereby the Examiner would voluntarily re-open prosecution) or by way of Petition to the Director (37 CFR 1.182). A petition in such

matters must be received by the Office no later than 2 months from the Office action in question. The non-examination of claims 32-35 as entered on 6/10/2009 (claims 32 and 33 were subsequently cancelled by Applicants) was inadvertent and regretful: had Applicants timely pointed out the discrepancy to the Examiner (e.g., prior to the filing of the RCE) the Examiner would have issued a supplemental final Office action in order to consider said claims on their merits. In the present case, Applicants did not timely request removal of the finality of the Office action dated 10/01/2009 and the subsequent filing of an RCE in this case renders such a request moot as the filing of the RCE automatically removes finality.

***Status of the Claims***

Claims 1, 5-16, 29-30 and 34-35 (claims 34 and 35 being added in the amendment submitted by Applicants on 06/10/2009) are pending in this application for US patent and were examined on their merits.

***Rejections Removed***

The rejection placed under 35 USC 112 First paragraph for Written Description (New Matter) in the previous Office action is hereby removed due to Applicants' amendment to claim 1 to state 'about 1.5 to 10%' rather than 'greater than 1.4% to about 10%. Support for is range is not explicitly stated in the Specification, however,

the disclosure as a whole indicates that Applicants were in possession of this range; e.g., the Specification discloses [0030] : 'addition of up to 10% by weight of silica' and [0055] teaches:'[the amount of silica used for example], is preferably in a range of about 0.5 wt. % to 10 wt. %, more preferably, about 1.5 wt. % to 7.5 wt. %.' Therefore, it is taken that the Specification provides sufficient evidence of conception of the newly-claimed range.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5-16 and 29-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,991,816 (reference provided in the IDS submitted by Applicants on 12/17/07) in view of Struengmann (US 6,284,269 ) in view of Mathowitz, E. (1999) in view of Esperester et al. (WO 01/28363 A1) in view of Abramovici et al. (US 6303626) in view of Saslawski et al. (US 6,426, 087).

Claims 1-8 of '816 teach a composition 'consisting essentially of' an aqueous red vine leaf extract and a pharmaceutical carrier.' Here, 'a pharmaceutical carrier' is not limited to one carrier as reading the phrase plainly, 'a pharmaceutical carrier' may mean numerous individual carriers which are combined to create 'a pharmaceutical carrier.' The claims (1-8) of '816 did not teach the specific carriers of the claimed invention, nor the specific amounts as claimed.

Struengmann (US 6,284,269 ) disclosed conventional tablet additives such as hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose (see example V/7, col's 10-11) as well as plasticizers such as polyethylene glycol (see claim 10). Thus, it was known that all of the tablet ingredients as Instantly claimed were conventional tablet ingredients, known at the time the invention was made.

Mathowitz, E. (1999) disclosed the conventional practice of addition of controlled-release coatings (films) in tablet manufacture (see pages 302 and 306-309).

Abramovici et al. (US 6303626) disclosed a tablet comprising 2% anhydrous colloidal silica, 2.1% active ingredient and the remainder consisting of conventional excipients (see, e.g., Example 9, col. 12). See also, Example 11, where they disclose a tablet comprising 2% anhydrous colloidal silica and 12.5% active ingredients, with the remainder of the tablet being conventional excipients (see Col. 13).

Esperester et al. (WO 01/28363 A1) taught oral compositions such as capsules and tablets comprising an aqueous extract of red vine leaf for treatment of venous insufficiency:

> In a preferred embodiment, the dietary supplement is in a form suitable for oral administration, in particular in a solid dosage form, i.e. **a capsule or tablet, that consists of 20 to 60% of aqueous red vine leaf extract with a high flavonoid content of 2-15%**. Another preferred dosage form is that of drops containing 3 to 90% of extract. Further suitable administration forms may be coated tablets, syrups, or the like (see p. 3).... ..... **For the preparation of solid dosage forms the thick extract is dried, for instance by use of a vacuum drying oven or a vacuum drying conveyer. Carriers or excipients may be added during drying to facilitate further processing of the extract. Such carriers or excipients may be silicon dioxide, maltodextrine, glucose syrup, cellulose and others** (see paragraph bridging pp. 4-5, emphasis added).

It is noted that silicon dioxide is colloidal silica. Also, it is clear that because the carriers are added during drying, that the silica and other carriers are in dried form, and

more than likely in powdered form even though the reference does not explicitly teach that the carriers are in powdered form.

It is apparent that Esperester et al. clearly taught drying of the extract prior to admixing into a tablet with a carrier such as silicon dioxide (colloidal silica).

Also, please see claims 1-15 and especially claim 9 which states:

9. A method according to claim 8 wherein said red vine leaf extract is present within the range of 1 to 50% related to the total mass of the dietary supplement composition.

Saslawski et al (US 6,426, 087) teaching preferred methods for compounding their medicinal tablets :

**(67) As a guide, the quantity of gastro-resistant film-coating excipients varies between 0.5 and 9% by weight of the tablet.**

(68) **These tablets may be bare, but are preferably film-coated. The film-coating envisaged will make it possible to avoid an unpleasant taste by bringing about masking of the taste.** It may participate in modifyIng the release of the active ingredient and/or of the promoting agent. **A gastro-resistant film-coating will make it possible to avoid any release in the stomach; a film-coating which is more hydrophobic and insensitive to pH** variations will contribute more towards extending the kinetics of dissolution. Depending on the role attributed to the film-coating, persons skilled in the art will be able to choose the film-forming agent from among the following categories: cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), ethyl cellulose, cellulose acetophthalate, cellulose acetopropionate, cellulose trimelliate, the polymers and copolymers of methacrylic acid and its derivatives. The film-forming agent may be supplemented with: plasticizers (such as polyoxyethylene glycols of high molecular weight, esters of polyacids such as citric acid or phthalic acid) fillers (such as talc, metal oxides such as titanium oxide) colorants chosen from those usable and approved by the pharmaceutical and food industries.

Hence, one of ordinary skill in the art would have been motivated to use a film coating between 0.5 and 9%, a range which overlaps with applicants' claimed range of 'greater than 1.4 to 10%' in order to hinder unpleasant taste and to ensure that the pharmaceutically active aqueous red vine extract was not degraded in the stomach thus ensuring better bioavailability of the active ingredient. It would have been obvious to create a tablet comprising aqueous red vine leaf extract with an enteric coating in order to shield the active ingredients of the extract from the acidic environment of the stomach in order to allow the active ingredients to pass undestructed into the small intestine for absorption into the bloodstream. It is clear from the teachings of Bilgrami et al. that the active ingredients enter into the bloodstream. Therefore, one of ordinary skill in the art would have easily recognized that protection of the extract would have been advantageous in order to prevent the degradation of the active components in order to optimize the effectiveness of the medicinal extract. Use of tablet films to protect tablet disintegration in the stomach were well-known and known to be used in the amounts as Instantly claimed and thus, the concept as claimed is not deemed inventive in view of the combined teachings of the prior art.

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the

art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal concentrations of components because concentration of aqueous red vine leaf extract is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. Although the prior art do not teach the particular combination of carriers which are added to the red vine extract or all the various permutations of concentration ranges as claimed, it would be conventional and within the skill of the art to identify the optional concentrations of a given excipient because (1) the selection of appropriate concentration of excipients to stabilize red vine extract for the intended purpose of preventing its denaturation and decomposition during storage are conventional and within the skill in the art, and (2) hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose and polyethylene glycol are well known in the art as excipients to used for tableting active ingredients. The incorporation of known active ingredients into tablets with conventional carriers was well within the purview of the ordinary artisan at the time the invention was made, and is hence considered *prima facie* obvious.

Applicants argue that this rejection is obviated due to their contention that the arguments against the rejection placed under 35 USC 103(a) are sufficient to overcome

the rejection under 35 USCV 103(a) which also pertain to this Double Patenting rejection. However, said arguments are not found convincing with regard to the rejection placed under 35 USC 103(a) and are thus concurrently not found convincing to overcome this Double Patenting rejection.

***Claim Rejections - 35 USC § 103***

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-16 and 29-30 remain rejected and claims 34 and 35 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Esperester et al. (WO 01/28363 A1) in view of Bilgrami et al. (1993) in view of Struengmann (US 6,284,269 ) in view of Mathowitz, E. (1999) in view of Saslawski et al. (US 6,426, 087) in view of Abramovici et al. (US 6303626) and in view of Lieberman, H., Ed. et al. (1990).

Esperester et al. (WO 01/28363 A1) taught oral compositions such as capsules and tablets comprising an aqueous extract of red vine leaf for treatment of venous insufficiency:

> In a preferred embodiment, the dietary supplement is in a form suitable for oral administration, in particular in a solid dosage form, i.e. **a capsule or tablet, that consists of 20 to 60% of aqueous red vine leaf extract with a high flavonoid content of 2-15%.** Another preferred dosage form is that of drops containing 3 to 90% of extract. Further suitable administration forms may be coated tablets, syrups, or the like (see p. 3).... ..... **For the preparation of solid dosage forms the thick extract is dried, for instance by use of a vacuum drying oven or a vacuum drying conveyer. Carriers or excipients may be added during drying to facilitate further processing of the extract. Such carriers or excipients may be silicon dioxide, maltodextrine, glucose syrup, cellulose and others** (see paragraph bridging pp. 4-5, emphasis added).

It is noted that silicon dioxide is colloidal silica and is anhydrous (silicon dioxide does not contain water). Also, it is clear that because the carriers are added during drying, that the silica and other carriers are in dried form, and more than likely in

powdered form even though the reference does not explicitly teach that the carriers are in powdered form.

It is apparent that Esperester et al. clearly taught drying of the extract prior to admixing into a tablet with a carrier such as silicon dioxide (colloidal anhydrous silica).

Also, please see claims 1-15 and especially claim 9 which states:

> 9. A method according to claim 8 wherein said red vine leaf extract is present within the range of 1 to 50% related to the total mass of the dietary supplement composition.

Pertaining to claims 34 and 35 which state that the red vine leaves are collected when the flavonoids have reached an optimum, drying and crushing the leaves, cutting the leaves to pieces, extracting the leaves with water from 60˚C to 80˚ C for 6 to 10 hours, concentrating and drying the extract and adding up to 10% by weight of colloidal anhydrous silica:

Esperester et al. specifically taught that their aqueous red vine leaf extract was made by collecting leaves when the flavonoids had reached an optimum, whereby the leaves are dried and crushed, cut to pieces and extracted at a temperature from 60˚C to 80˚ C for 6 to 10 hours (e.g., via percolation) and concentrated via evaporation and dried (e.g., by use of a vacuum dryer) (see p. 4, line 18- p. 5, line 2).

Esperester et al. did not specifically disclose an embodiment which included colloidal silica and an aqueous extract of red vine leaf in the claimed amounts, a binder such as microcrystalline cellulose, a filler such as hydrogen phosphate or magnesium stearate, a plasticizer, a colorant or the particular amounts of each constituent in the tablet.

Bilgrami et al. (1993) studied the preventative effects of aqueous *Vitis vinefera* L. leaf. (red vine leaf) on nephrotoxicosis due to ingestion of the micotoxin citrinin. Bilgrami et al. discovered that *V. vinefera* L. leaf water extract administered by intubation to albino Swiss mice challenged with citrinin possessed greater toxicity prevention than cortisone (see entire reference, especially Table 1 and p. 482, col. 2). Hence, prior to Applicants' Invention, aqueous red vine leaf extract was a composition with known pharmaceutical value.

Struengmann (US 6,284,269 ) disclosed conventional tablet additives such as hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose (see example V/7, col's 10-11) as well as plasticizers such as polyethylene glycol (see claim 10). Thus, it was known that all of the tablet ingredients as Instantly claimed were conventional tablet ingredients, known at the time the invention was made.

Mathowitz, E. (1999) disclosed the conventional practice of addition of controlled-release coatings (films) in tablet manufacture (see pages 302 and 306-309). "Coatings often contain several components in addition to the primary component polymeric species, which provides the backbone of the coating. Some of the secondary coating components may be deliberately added in order to modify the permeability of the primary polymer by providing channels or pores within the coating...Other materials, such as plasticizers, although they are added for entirely different reasons, can, in some instances, significantly modify drug release rates.." (p. 302, Col. 1). "The outer coating protects the drug until the small intestine is reached. The inner coating...is of such a thickness and composition that the drug is released in the colon. Multilamellate coatings in which each coating has a different function to perform offer the potential of developing very sophisticated, controlled release coating system." (*Id*). See Table 1 for conventional materials such as coatings and plasticizers used in tablet films (p. 307). Additionally, Mathowitz further taught "Coatings may well contain other components, such as colors or antioxidants, but specific attention is not given to components the primary function of which is not covered by one of these three categories."

Mathowitz discloses all of the claimed tablet film components; e.g., claim 15 comprises 1) a film former: Applicants' specification indicates that a preferred film former is hypromellose. Hypromellose is short for 'hydroxypropyl methylcellulose which is disclosed by Mathowitz as a coating (see Table 1), 2) a plasticizer: Table 1 of

Mathowitz discloses 9 types of conventional plasticizers, 3) a 'coating' agent: See enteric coatings in Table 1 of Mathiowitz (these are all coating agents) and 4) a coloring agent which is taught by Mathowitz at p. 307, col. 1 (as recited above).

Saslawski et al. (US 6,426, 087) taught a galenic formulation of guanylguanidine (see Abstract and Claims). This Patent by Saslawski et al. teaches various conventional means for tableting a pharmaceutical preparation; for example, Saslawski et al. explain that:

> It may also be noted that the pharmaceutical dosage forms of the invention ensure excellent reproducibility of the results, while allowing increased control of the rate of release during the phase of prolonged release of the active ingredient. By using the pharmaceutical dosage forms of the invention, it becomes **possible to optimize the availability of the active ingredients in the body taking into account both the tolerance of the subject to the active ingredient and the pharmacokinetic and metabolic profiles of the active ingredient.**
>
> (10) The tablets of the invention are moreover advantageous from the point of view of the formulation of the active ingredients since a judicious choice of the excipients leads to tablets with high concentrations of active ingredients.
>
> The tablets according to the invention may comprise, in combination with the absorption-promoting agent, one or more additional excipients so as to obtain mono- or polyphase tablets. **Persons skilled in the art will choose these excipients according to the desired final properties, the application envisaged or so as to overcome a disadvantage linked to the method of manufacturing the tablets.**
>
> (56) These excipients exist especially among the following categories: diluents, binders, lubricants, antioxidants, colorants, sweeteners, flavourings and acidulants, wetting agents, hydrophilizing agents such as sorbitol and cyclodextrins, osmotic agents such as mannitol, pH regulators, stabilizing agents such as trehalose and mannitol, adsorbants, chelating and sequestering agents and gastro-resistant film-coating excipients of the type including cellulose acetyl phthalate and polymethacrylates.
>
> By way of example, any one of the following diluents or a combination

thereof may be chosen: calcium carbonate, calcium sulphate, sucrose, dextrates, dextrin, dextrose, dicalcium phosphate dihydrate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, cellulose, microcrystalline cellulose, sorbitol, starches, pregelatinized starch, talc, tricalcium phosphate and lactose.

(58) Among the binders, there may be mentioned: gum arabic, gum tragacanth, guar gum, alginic acid, sodium alginate, sodium carboxymethylcellulose, dextrin, gelatin, hydroxyethylcellulose, hydroxypropylcellulose, liquid glucose, magnesium and aluminium silicate, maltodextrin, povidone, pregelatinized starch, starch and zein.

(59) The lubricants are glidants (such as anhydrous silicate, magnesium trisilicate, magnesium silicate, cellulose, starch, talc or tricalcium phosphate) or alternatively antifriction agents (such as calcium stearate, hydrogenated vegetable oils, paraffin, magnesium stearate, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, fumaric acid, stearic acid or zinc stearate and talc).

(63) Examples of adsorbants are bentonite, anhydrous colloidal silica, kaolin, magnesium and aluminium silicate, microcrystalline cellulose and cellulose.

(65) The quantities of these additives are those usually used in the art. In general, the binder may represent from 0.5 to 25% by weight, or better still from 2 to 5% by weight of the tablet.

(66) The lubricants are preferably incorporated into this tablet in an amount of 0.01 to 10% by weight.

(67) **As a guide, the quantity of gastro-resistant film-coating excipients varies between 0.5 and 9% by weight of the tablet.**

(68) **These tablets may be bare, but are preferably film-coated. The film-coating envisaged will make it possible to avoid an unpleasant taste by bringing about masking of the taste.** It may participate in modifying the release of the active ingredient and/or of the promoting agent. **A gastro-resistant film-coating will make it possible to avoid any release in the stomach; a film-coating which is more hydrophobic and insensitive to pH** variations will contribute more towards extending the kinetics of dissolution. Depending on the role attributed to the film-coating, persons skilled in the art will be able to choose the film-forming agent from among the following categories: cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), ethyl cellulose, cellulose acetophthalate, cellulose acetopropionate, cellulose trimelliate, the polymers and copolymers of methacrylic acid and its derivatives. The film-forming agent may be supplemented with: plasticizers (such as polyoxyethylene glycols of high molecular weight, esters of polyacids such as citric acid or phthalic acid) fillers (such as talc, metal oxides such as titanium oxide) colorants chosen from those usable and approved by the

pharmaceutical and food industries.

(69) The tablets of the invention are conventionally prepared by a method including the steps of granulation followed by compression. More precisely, the method of manufacture which is the subject of the invention comprises the steps consisting in: a) preparing a granule of an active substance from a pulverulent mixture of the active substance, to which there would have been added the absorption-promoting agent, preferably in liquid form, agents modifying the kinetics of dissolution, a binding agent and any other excipient which persons skilled in the art will judge to be necessary. The granule formed is called the inner phase. b) preparing, where appropriate, a pulverulent mixture, termed outer phase, comprising for example cohesion agents, glidants, lubricants. c) combining, by mixing, the inner and outer phases. It should be noted that all of the constituents of the outer phase may be added and mixed with the excipients of the inner phase during the preparation of the granule ready to be compressed. d) forming the tablet by compressing the mixture.

(70) Step (a) involves the granulation of powders of amorphous or crystallized particles. This granulation is carried out in a manner known per se and, for example, by a wet granulation method.

(71) The granulation method comprises five essential steps: (i) dry mixing of the various constituents, (ii) wetting, (iii) actual granulation, (iv) drying, and then (v) sizing.

(72) The dry mixing consists of mixing the pulverulent excipients entering into the composition of the granules.

(73) The wetting consists of adding to the pulverulent mixture the various constituents, a wetting liquid which may be water, or an aqueous or organic solution of binder or an alcohol. This is carried out in a mixer-kneader of the planetary, roller, projection or whirling type or a mixer-granulator of the rapid type.

(74) In step (a), the appropriate wetting liquid is water or an alcohol or an aqueous or organic solution of binder, as generally recommended in the art.

(75) According to a particularly preferred embodiment, the absorption-promoting agent is used as wetting liquid for the granulation.

(76) The drying may be carried out in an oven, or in a fluidized air bed dryer, or by microwave.

Abramovici et al. (US 6303626) disclosed a tablet comprising 2% anhydrous colloidal silica, 2.1% active ingredient and the remainder consisting of conventional excipients (see, e.g., Example 9, col. 12). See also, Example 11, where they disclose a tablet comprising 2% anhydrous colloidal silica and 12.5% active ingredients, with the remainder of the tablet being conventional excipients (see Col. 13).

Lieberman, H.A., Ed. et al. taught that granule strength and friability of tablets were dependent upon the base materials (i.e., carriers):

> A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. the strength of a wet granule is due mainly to the surface tension of liquid and capillary forces...Upon drying, the dried granule will have strong bonds resulting from fusion or recrystallization...Measurements of granule strength are, therefore, aimed at estimating the relative magnitude of attractive forces seeking to hold the granule together. The resultant strength of a granule is, of course, dependent upon the base material, the kind and amount of granulating agent used, the granulating equipment used and so on." (p. 308)

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal concentrations of

components because concentration of aqueous red vine leaf extract is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. Although the prior art do not teach the particular combination of carriers which are added to the red vine extract or all the various permutations of concentration ranges as claimed, it would be conventional and within the skill of the art to identify the optional concentrations of a given excipient because (1) the selection of appropriate concentration of excipients to stabilize red vine extract for the intended purpose of preventing its denaturation and decomposition during storage are conventional and within the skill in the art, and (2) hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose and polyethylene glycol are well known in the art as excipients to used for tableting active ingredients, colloidal anhydrous silica being a carrier specifically disclosed by Esperester et al. as being suitable for adding to aqueous red vine leaf extracts while drying to produce pharmaceutical dosage forms. The incorporation of known active ingredients into tablets with conventional carriers and adjusting the amounts of these carriers was well within the purview of the ordinary artisan at the time the invention was made, and is hence considered *prima facie* obvious.

Hence, it naturally follows that the use of 10% colloidal anhydrous silica (claim 34) is deemed an obvious variation of the teaching of Esperester et al. in view of the secondary references.

Although Esperester et al. did not disclose an explicit embodiment which showed a tablet comprising the claimed amounts of red vine leaf aqueous extract and colloidal silica, Esperester et al. clearly strongly suggested such a combination in that they plainly taught that a capsule or tablet comprising 20-60% of red vine leaf aqueous extract was advantageously added to a carriers such as silicon dioxide (colloidal silica) to make into tablets/capsules. Thus, it is clear that the tablet proposed by Esperester et al. would have contained from 40-80% carriers for the tablet. Although Esperester et al. did not specifically teach the amounts of the silica or cellulose as Instantly claimed, it is clear that because the capsule or tablet contained from 20 to 60% of the active ingredient (i.e., the aqueous extract of red vine leaves) that the carrier could have been present in an amount from 40-80% of the tablet. It is deemed that the adjustment of concentration of the carriers with respect to the active ingredients and other suitable carriers would have been well within the purview of the ordinary artisan at the time the invention was made because such adjustments were considered conventional in the art of pharmacology, especially considering that amounts of colloidal anhydrous silica for use in pharmaceutical compounding were known according to Abramovici et al. who incorporated 2% of this excipient into their tablet.

Although Esperester et al. did not disclose wherein the tablet was manufactured with 1-3% of a film, tablet filming was a conventional practice in the art for necessitating drug delivery to the small intestines. Clearly, as taught by Saslawski et al.:

**(67) As a guide, the quantity of gastro-resistant film-coating excipients varies between 0.5 and 9% by weight of the tablet.**

(68) **These tablets may be bare, but are preferably film-coated. The film-coating envisaged will make it possible to avoid an unpleasant taste by bringing about masking of the taste.** It may participate in modifying the release of the active ingredient and/or of the promoting agent. **A gastro-resistant film-coating will make it possible to avoid any release in the stomach; a film-coating which is more hydrophobic and insensitive to pH** variations will contribute more towards extending the kinetics of dissolution. Depending on the role attributed to the film-coating, persons skilled in the art will be able to choose the film-forming agent from among the following categories: cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), ethyl cellulose, cellulose acetophthalate, cellulose acetopropionate, cellulose trimelliate, the polymers and copolymers of methacrylic acid and its derivatives. The film-forming agent may be supplemented with: plasticizers (such as polyoxyethylene glycols of high molecular weight, esters of polyacids such as citric acid or phthalic acid) fillers (such as talc, metal oxides such as titanium oxide) colorants chosen from those usable and approved by the pharmaceutical and food industries.

Hence, one of ordinary skill in the art would have been motivated to use a film coating between 0.5 and 9%, a range which overlaps with applicants' claimed range of 'greater than 1.4 to 10%' in order to hinder unpleasant taste and to ensure that the pharmaceutically active aqueous red vine extract was not degraded in the stomach thus ensuring better bioavailability of the active ingredient. It would have been obvious to create a tablet comprising aqueous red vine leaf extract with an enteric coating in order to shield the active ingredients of the extract from the acidic environment of the stomach in order to allow the active ingredients to pass undestructed into the small intestine for absorption into the bloodstream. It is clear from the teachings of Bilgrami et al. that the active ingredients enter into the bloodstream. Therefore, one of ordinary skill in the art

would have easily recognized that protection of the extract would have been advantageous in order to prevent the degradation of the active components in order to optimize the effectiveness of the medicinal extract. Use of tablet films to protect tablet disintegration in the stomach were well-known and known to be used in the amounts as Instantly claimed and thus, the concept as claimed is not deemed inventive in view of the combined teachings of the prior art.

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal concentrations of aqueous red vine leaf extract because this extract is an art-recognized result-effective variable (i.e., having an advantageous effect on venous insufficiency) which would have been routinely determined and optimized in the pharmaceutical art. Although the claimed invention is not explicitly found in the prior art, the choice of carriers as Instantly claimed is deemed to be merely a matter of design choice. According to the prior art, especially established by Lieberman, H.A., Ed. et al. in addition to Saslawski et al., compounding of pharmaceuticals into tablets was routine and within the skill of the ordinary artisan at the time the invention was made. All of the carriers as Instantly claimed were recognized conventional carriers/additives for pharmaceutical tablets, most of the claimed compounds already

being recognized for use in pharmaceutical tablets, some within the ranges set forth in Applicants' claims.

As taught by Saslawski et al.:

> It may also be noted that the pharmaceutical dosage forms of the invention ensure excellent reproducibility of the results, while allowing increased control of the rate of release during the phase of prolonged release of the active ingredient. By using the pharmaceutical dosage forms of the invention, it becomes **possible to optimize the availability of the active ingredients in the body taking into account both the tolerance of the subject to the active ingredient and the pharmacokinetic and metabolic profiles of the active ingredient.**
>
> (10) The tablets of the invention are moreover advantageous from the point of view of the formulation of the active ingredients since **a judicious choice of the excipients leads to tablets with high concentrations of active ingredients.**
>
> The tablets according to the invention may comprise, in combination with the absorption-promoting agent, one or more additional excipients so as to obtain mono- or polyphase tablets**. Persons skilled in the art will choose these excipients according to the desired final properties, the application envisaged or so as to overcome a disadvantage linked to the method of manufacturing the tablets.**

Further in view of Lieberman, H.A., Ed. et al. who taught that granule strength and friability of tablets were dependent upon the base materials (i.e., carriers), it is clear that the choice of type and percentage of particular carrier for use in pharmaceutical tablets are result effective, meaning that each carrier contributes to the tablets overall strength and cohesiveness. This variability is clearly additionally associated with the components of tablet films as taught by Mathiowitz. Accordingly, it would have been conventional and within the skill of the art to identify the claimed concentrations of given tablet excipients and film components because (1) the

selection of appropriate concentration of excipients and film components to stabilize red vine extract for the intended purpose of preventing its denaturation and decomposition during storage and to optimize drug delivery are conventional and within the skill in the art , and (2) hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose and polyethylene glycol are well known in the art as excipients to used for tableting active ingredients. The incorporation of known active ingredients into tablets with conventional carriers was well within the purview of the ordinary artisan at the time the invention was made, and is hence considered *prima facie* obvious.

It is the opinion of the Examiner that the claimed invention is an obvious variation of the compositions disclosed by Esperester et al. and/or Bilgrami et al. respectively and is thus unpatentable. The carriers which are added to the known, medicinal product of an aqueous extract of red vine leaf were well-known in the art as conventional tableting excipients and thus, the addition of such known excipients and concentration adjustment thereof is deemed plainly obvious to one of ordinary skill in the art of pharmaceutical compounding. [If]... there are [a] finite number of identified, predictable solutions, [a] person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 U.S. 2007.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Response to Arguments***

Applicants' arguments have been fully considered, but are not found persuasive.

Applicants traverse the Examiner's lack of finding of an unexpected result concerning the Declaration filed by Inventor Anke Esperester on 9/25/2008 and assert that 'Adding colloidal anhydrous silica **during** the step of drying the red vine leaf extract gave from 2 to 4-5X better stability" (pp. 7-8, Remarks, emphasis in Applicants' original remarks). However, again, Esperester et al. taught the addition of colloidal anhydrous silica during the step of drying (p. 4, line 32- p.5, line 2).

Applicants argue: "...applicant's tablets showed unexpectedly superior storage stability characteristics..." which are "...unrelated to, and not predictive of, the storage stability of the applicant's tablets. Chang teaches the use of silica for enhancing the crushing stability, i.e., stability against moisture air, and temperature. Such stabilities

are not interrelated and thus one skilled in the art viewing Chang would not contemplate the use of silica for anything other than enhancing crushing stability, let alone for improving storage stability" (p. 8, Remarks).

However, Applicants' assertions are unsubstantiated and are respectfully not found convincing. Again, Lieberman, H.A., Ed. et al. taught that granule strength and friability of tablets were dependent upon the base materials (i.e., carriers):

> A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. the strength of a wet granule is due mainly to the surface tension of liquid and capillary forces...Upon drying, the dried granule will have strong bonds resulting from fusion or recrystallization...**Measurements of granule strength are, therefore, aimed at estimating the relative magnitude of attractive forces seeking to hold the granule together. The resultant strength of a granule is, of course, dependent upon the base material, the kind and amount of granulating agent used, the granulating equipment used and so on.**" (p. 308, emphasis added)

Thus, the crushing strength (e.g., granule strength) is related to disintegration as are extrinsic parameters such as moisture, air and temperature. Hence, the amount of colloidal silica is directly related to the cohesion or hardness or in otherwords, the disintegration (rate) of the tablet.

Of course, tablet disintegration will also be dependent upon the active ingredient present in the tablet as well as additional carriers also present in the tablet as Cheng et al. state "addition of lubricant and glidant in the formulation may allow reduced

particulate friction and increased densification to take place, which leads to an increased tablet crushing strength." Tablet disintegration will be based in part upon the hardness of the table:; clearly a harder tablet; i.e., a denser tablet with high adhesion forces will disintegrate less-readily than a tablet with low adhesion and having a lower density (and hence will also be less hard).

Again, the Declaration, in the opinion of the Examiner does not provide any evidence of an unexpected result. While Declarant indicates that drying the aqueous extract in the presence of anhydrous colloidal silica results in a tablet which has unexpectedly superior disintegration properties, the results found in the Declaration are not considered superior; rather, the results are decidedly expected based upon the knowledge that aqueous red vine leaf extract was advantageously dried in the presence of a carrier such as colloidal anhydrous silica and because addition of colloidal anhydrous silica to pharmaceuticals was known to increase tablet strength which would attribute to decreased disintegration.

Applicants data thus tends to show that the addition of 35mg of colloidal anhydrous silica to the drying process of red vine extract shows better stability over a similar composition whereby the red vine extract was not dried with colloidal anhydrous silica. This is expected. Chang et al. reported the 'dramatic enhancement of the crushing strength' of DMP 504 powder tablets upon admixture with silicon dioxide (colloidal anhydrous silica) (see entire reference, especially pp. 287 and 289). Chang et

al. explained that the possible reasons for the increase in tablet hardness due to adding colloidal silicon dioxide are "(a) reducing the negative bonding effect of lubricant by stripping off magnesium stearate from the surface of the host particles, (b) facilitating densification of the powder mixture because of the glidant action....*Because the crushing strengths for tablets with 0.5 and 1% magnesium stearate at five compression forces are identical, increase in tablet hardness most likely is due to the facilitated densification via the glidant effect of colloidal silicon dioxide.*" (p. 288, emphasis added). Overall, Chang et al. concluded that "[t]he improved flow properties and reduced tablet thickness by the addition of colloidal silicon dioxide in the tablet formulation provide the evidence for the increased tablet hardness through the facilitated densification. Therefore, Cheng et al. is additional evidence that the results exhibited in the Declaration do not show any evidence of an unexpected result; rather, they show that the addition of 35mg of colloidal anhydrous silica to red vine leaf provides for better stability which is expected and made obvious by the prior art.

Applicants argue that the "...2 mg difference in the solution prior to spray drying is not significant in light of the additional 15 mg of colloidal anhydrous silica added to the red vine extract of Formulation II **during** the drying step." However, Applicants' remarks are unsubstantiated and do not provide evidence that this discrepancy would not be significant. Statements of what one of skilled in the art would or would not expect is not evidence thereof (Remarks, p. 8). Applicants have not explained why there is such a large discrepancy between the amount of silica between the first and second tablet

when clearly, the variable being studied is the silica added to the red vine extract while being dried. Further, Applicants again stress that the silica is added during the drying step; however, Esperester et al. clearly taught addition of colloidal anhydrous silica during the drying step even though they did not explicitly teach the amount of silica as claimed.

Applicants disagree with the Examiner's statement that there is a 'very large discrepancy' between the amount of crospovidone between the tested formulations in the Declaration and assert "..the improved stability in a tablet having both colloidal silica and the additional disintegrant is even more unexpected as one skilled in the art would reasonably conclude that tablets having additional disintegrants would have reduced stability." (p. 9, Remarks). However, again, Cheng et al. taught that in some cases, "addition of lubricant and glidant...may allow reduced particulate friction and increased densification to take place, which leads to an increased tablet crushing strength." Hence, Applicants remarks are not persuasive to demonstrate that the discrepancy of crospovidone did not attribute (in some amount) to the disintegration rate of the formulation.

Compounding pharmaceutical tablets to achieve maximum parameters such as friability and strength, which contribute to overall disintegration time and therefore stability is well-known, conventional protocol in the pharmaceutical art. "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton *KSR* 127S. Ct. at

1742. Achieving a disintegration time which is more or less than another tablet having different excipients or a tablet manufactured by a different means is *expected* based upon the knowledge stemming from pharmaceutical tablet manufacture. Hence, Applicants data which shows 'enhanced' stability is not sufficient to support an *unexpected* result to obviate this rejection. This is especially in addition to the fact that colloidal anhydrous silica was already shown to have tablet hardening capabilities (Cheng et al.,*supra*).

What is expected is that the addition of colloidal anhydrous silica to a powder formulation for making tablets will provide for a dose-dependent linear increase in stability relative to the amount of added colloidal anhydrous silica according to Cheng et al.

To again reiterate from the previous Office action, Applicants' invention is, in the opinion of the Examiner, an obvious modification of the prior art. The prior art already taught the medicinal effects of an aqueous extract of red vine. While Applicants have compounded this known, medicinal extract into a tablet which is not explicitly known in the art, tablets containing aqueous red fine leaf extract were already known in the art, and further known to be dried in the presence of carriers such as colloidal silica (silicone dioxide is anhydrous) as taught by Esperester et al. (WO 01/28363 A1). Moreover, the excipients used by Applicants are well-known, conventional excipients used routinely in the prior art for tablet manufacture. The use of these specific percentages of known,

conventional excipients to prepare a tablet with enhanced stability was within the skill level of the ordinary artisan at the time the invention was made; and according to the prior art, stability of tablets was a parameter which was routinely optimized. Thus, it plainly follows that the selection of types and amounts of known carriers to produce a desired disintegration rate would have been routine protocol in the manufacture of pharmaceutical tabletting. The invention *as a whole* is deemed obvious from the prior art; in that there is no one novel concept present in the claimed invention which would render the claimed invention patentable. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301

The Supreme court has acknowledged that:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. **If a person of ordinary skill can implement a predictable varition..103 likely bars its patentability**...if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions...
>
> ...**the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results** (see *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 U.S. 2007) emphasis added.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia Leith whose telephone number is (571) 272-0968. The examiner can normally be reached on Monday - Friday 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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